Remarks

Applicant affirms its election of Group 1A, claims 34-42 for prosecution in the present application. Applicant reserves the right to file a divisional application to the non-elected subject matter.

The informalities of claims 34 and 42 have been corrected. Thus, the objection to these claims should be withdrawn.

The Office Action rejected claims 34-42 as being unpatentable over combination of Ozanich (US 2002/0011567) and Rollins et al (US 2003/0137669). For the reasons enumerated below, these references do not render the claims unpatentable under 35 U.S.C. §103(a).

Ozanich teaches a fiberoptics apparatus for measuring the optical absorption spectrum of N—H, C—H and O—H characteristic to fruit. The signals derived from these absorption spectra are based on molecular vibration, infrared, IR, spectroscopy to assess the bond energies of these molecules. Thus detection optical fibers can be used to detect differences compared to the illuminating fiber to enhance its signal-to-noise ratio of the absorption spectra. The system will work when the object and signal are stationary. The Rollings tissue imaging system utilizes a spatial interference technique. The signal is mixed with a signal generated from a delay line to produce interference images. Again these images are stationary and the sample is stationary. Additionally, the size of the optical fibers as well as their geometrical configuration are not crucial to obtain the IR absorption spectra of fruit in the Ozanich apparatus or the images in Rollings apparatus. The central core illuminating fiber surrounded by six detection fibers used by Ozanich was likely one of convenience, not of necessity. In contrast, the present invention measures the frequency of a subsonic oscillation of micron-sized cilia compared to their cellular base. We apply temporal optical modulation of the incident optical frequency by optical mixing of the back scattering photons from the cilia which are Doppler shifted because of the oscillatory nature of the cilia. i.e., we apply temporal optical modulation of the incident optical frequency by optical mixing of the back scattering signals. The back-scattered signals from the cilia are dynamic and nonstationary. They are mixed with the backscattered light

from the tissue cell bodies from the measured sample. This optical mixing is necessary to utilize dynamic laser light scattering to measure the ciliary activity continuously in time. These optical signals do not arise from characteristic molecular oscillations in the infrared range. They are generated from light scattering from the cilia which under go an oscillatory movement in the subsonic frequency range. These dynamic back scattering signals are nonstationary. This non-stationality originates from ciliary activity in the measured region of interest. Ciliary beating is nonstationary with a height function generally less than 10 microns and with a coordinated metachronal field generally less than 100 microns. To achieve optimal optical mixing, it is necessary to measure the ciliary activity continuously in time using dynamic laser light scattering in a field of smaller dimensions than that of a metachronal wave. If larger fields of ciliated epithelia are used, the signals from multiple metachronal fields will likely result in a very diffuse heterodyne signal. In our apparatus, heterodyne modulation and optical mixing within a metachronal field can only be achieved with 4 micron core, 125 micron or less clad single mode, 633 nm optical fiber arranged in an optical configuration and spatial geometry of the incident and collection fibers as shown in Fig 3 of this patent application. This configuration together with the independent and matching photon counting units used for each fiber as well as nonstationary signal processing are required to measure ciliary activity dynamically and continuously. The method and the apparatus described in the subject patent application are the only method and apparatus that fulfills these criteria. A combination of the Ozanich the and Rollings technologies or methods will not work. Thus our concepts and technology contained within the subject patent are novel and non-obvious to a person skilled in the art and claims 34-42 are patentable.

Claims 34-42 have also been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,807,264 to Paltieli, in view of Yang, US Patent Pub No. 2002/0101593

For the reasons enumerated below, these references do not render claims 34-42 unpatentable.

Paltieli discloses an endoscope apparatus for measuring ciliary motion that comprises three optical fibers, a fiber for transmitting light to illuminate the body to be probed, and two optical fibers for receiving backscattered light from two spots on the epithelium. The difference between the signals obtained from the receiving fibers is used to cancel motion artifacts. Thus, the cancellation of motion artifacts occurs in their case only if the ciliary motion is a stationary signal during the course of the experiment. Most investigators in the field of measurement of ciliary motion, for simplicity, assume ciliary motion is stationary. This is consistent with the Paltieli illustration in Fig 9 of the frequency spectrum showing a dominant frequency of 4Hz. However, ciliary motion, as well as most biologically oscillatory motion, is non-stationary in nature. This non-stationary nature of ciliary motion is illustrated in Fig 8 and Fig 9 in the subject patent application. In Fig 8, we demonstrate that the signals derived from ciliary activity of a native ciliated epithelia comprise a low frequency envelop which is the metachronal wave frequency, which carries a high frequency non-stationary signal, which is the ciliary beat frequency. In Fig 9, we show that multiple frequencies are observed in ciliary activity *in vivo*. Because of this non-stationary nature of the ciliary motion, the only way to obtain an accurate measurement of ciliary motion is by use of a spatial map of ciliary motion on a distance scale less than the length of the metachronal wave field and at a specific time. We use a plurality of receiving fibers in close proximity to the illuminating fiber to produce a spatial map of ciliary motion over a limited field at a specific time. These together with the non-stationary signal analysis techniques employed provides the only system capable of producing such an analysis of ciliary motion. This nonstationary nature of ciliary motion is illustrated in Fig 10. Ciliary beat frequency can dynamically change from 4.5 Hz to 5.2 Hz to 10 Hz in a matter of seconds while the metachronal wave frequency may remain relatively constant. The Ozanich and Rollings patents neither take advantage of the power of non-stationary analysis nor of the close-set geometrical configuration of six detection fibers described in our patent. Nor would a combination the devices and concepts of Ozanich and Rollins result in a working system for the measurement of characteristics of ciliary beat frequency claimed in the subject patent, let alone a spatial map of these characteristics derived from a plurality of detectors. Those patents and technologies were dependent on a stationary

object and either molecular vibrations in the infrared frequency range or the interference imaging of stationary objects, respectively. Thus our device is novel and non-obvious.

Yang discloses a method of measuring the size and distribution of cellular characteristics based on interferometry technique. This system comprises an irradiated region of interest of the tissue sample with spatially coherent light having a beam with one wavelength and second beam with another wavelength. The reference light has the first wavelength and the second wavelength utilizes a variable path length to generate a interference heterodyne signal. As noted, such signal was then analyzed for the characterization of the motion of the cell nuclei using autocorrelation time as illustrated in Fig 6 and Fig 7. As with Paltiele, such an autocorrelation analysis fundamentally depends on the signal being stationary in nature. The motility of cell nuclei is dependent on the size of the scatterer which also governs the heterodyne signal as denoted in eq (5) in Yang's patent. The motility of the cell nuclei is derived from the rate of decay of the autocorrelation function of the heterodyne signal, which is again stationary in nature. A simultaneous plurality of spatial nature of vibration motion cannot be obtained using the Paltiele design. Thus, this system is fundamentally different from the subject patent application and does not contain the concepts or technologies contained within our patent. Thus, our device is novel and non-obvious.

Taken together, these references will not allow the development of a method for measuring ciliary activity (the sample) even if the oscillatory signal is stationary and the concepts contained in diverse devices for different applications are linked together. That these diverse applications share common features such as a single fiber surrounded by detection fibers, is coincidental, not disenabling, as the applications and concepts are quite different. Only a system with the confined geometrical constraint in the subject patent which makes a spatial map of the simultaneous oscillatory motions of cilia at single points in space and time, and each point on distance scales smaller than the length of the metachronal wave field can portray non-stationary signals contained within the special field of ciliary activity. The method and apparatus described in the subject patent application is the only method and apparatus that fulfills these necessary criteria.

For the above-noted reasons it is submitted that claims 34-42 as presently amended are patentable.

Respectfully submitted,

Martin L. Katz
Reg. No. 25,011

Wood, Phillips, Katz, Clark & Mortimer
500 West Madison Street
Suite 3800
Chicago, Illinois 60661-2511
T: 312/876-1800
F: 312/876-2020